REMARKS

Claims 1, 3-6, 8-15, 20, 24-27, 30 and 31 are pending in the instant application. Claims 1, 3-6, 8, 9, 11-15, 20, 27 and 30 stand rejected under 35 USC § 103(a) as being unpatentable over Yu [US 6103492] in view of Buck *et al* ["Photochemically induced dynamic nuclear polarization[…]" Biochemistry 77(9) pp5145-8]. Claim 10 stands rejected under 35 USC § 103(a) as being unpatentable over Yu [US 6103492] in view of Buck *et al* ["Photochemically induced dynamic nuclear polarization[…]" Biochemistry 77(9) pp5145-8], and further in view of Katahira et al. ["NMR studies of G:A mismatches in oligodeoxyribonucleotide duplexes modeled after ribozymes" Nucleic Acids Research, 1993, Vol. 21, No. 23, pp. 5418-5424]. Claims 24 and 25 are rejected under 35 USC 103(a) as being unpatentable over Yu, in view of Buck, and in further view of Obremski (6110749). Claim 26 is rejected under 35 USC 103(a) as being unpatentable over Yu in view of Buck, in further view of Pines *et al* (6426058). Claim 31 is rejected under 35 USC 103(a) as being unpatentable over Yu in view of Buck, in further view of Neild *et al* ("Uroscopy in the 21st Century: High-field NMR Spectroscopy" Neprol. Dial. Transplant. 1997; 12: 404-17). The application has been amended. Claims 1 and 6 have been amended. Applicant respectfully submits that none of the amendments introduce new matter in contravention of 35 U.S.C.§132. Reconsideration is respectfully requested.

Claims 1, 3-6, 8-9, 11-15, 20, 27 and 30 are rejected under 35 USC 103(a) as being unpatentable over Yu (6103492) in view of Buck *et al* ("Photochemically Induced Dynamic Nuclear Polarization Investigation of Complex Formation of the NH_2-terminal DNA-binding domain of *lac* repressor with Poly[d(AT)]" Biochemistry; 77(9): 5145-8). This rejection is respectfully traversed.

The present invention discloses an *in vitro* assay method to detect a change in a biological species. The assay reagent of the method of the invention comprises an NMR active nucleus selected from ^{15}N, ^{19}F, ^{31}P, ^{1}H, ^{29}Si and ^{13}C, which is hyperpolarized by dynamic nuclear polarization, comprising mixing the assay reagent with a paramagnetic

species (DNP agent) and/or a free radical generator or other particles having associated free electrons.

Yu discloses an NMR spectroscopy method for the detection of the interaction between an agent and a receptor, using signals derived from NMR-active nuclei such as ^{2}H, ^{13}C, ^{15}N, and ^{18}O (column 40 lines 37-45). NMR spectroscopy is used for the structural determination of a substance, i.e. it observes a static system. In support of this, please see enclosed entry for "spectroscopy" in "Oxford Dictionary of Biochemistry and Molecular Biology" 1997, which defines spectroscopy as a method used to investigate the chemical composition, molecular structure or atomic structure of a substance.

Yu also discloses an immunoassay for detecting the presence of a polypeptide in a biological sample (column 8 lines 45-59). The preferred indicators disclosed here include a radioactive label, a fluorogenic label, biotin or an enzyme. At the time of the present invention, the skilled person would have understood that an "assay" is used to detect the activity, potency, strength, etc., of a substance in comparison with a standard (see enclosed entries for "assay", "bioassay", and "immunoassay" from "Oxford Dictionary of Biochemistry and Molecular Biology" 1997). An assay therefore observes something dynamic.

Applicant respectfully submits that combining the above-described teachings to support that Yu teaches an immunoassay having an NMR active nucleus is incorrect. In the teachings relating to an assay, Yu does not teach use of an NMR active nucleus as an indicator in an assay, e.g. as taught for e.g., a radioactive label or a fluorogenic label.

Furthermore, Yu does not teach hyperpolarizing the NMR active nuclei using dynamic nuclear polarization comprising mixing the assay reagent with a paramagnetic species (DNP agent) and/or a free radical generator or other particles having associated free electrons.

Applicant respectfully submits that the deficiencies of Yu are not resolved by the teachings of Buck.

Buck teaches an NMR spectroscopy method for observing binding of the *lac* repressor with poly[d(AT)]. The NMR signal intensity in the method of Buck is enhanced by attacking the side chains of the aromatic amino acids tyrosine, histidine and tryptophan with a photoexcited dye.

As submitted above in relation to Yu, it is Applicant's submission that an NMR spectroscopy method as carried out by Buck is not an assay as would have been understood by the skilled person at the time of the invention.

Furthermore, the dynamic polarization method of Buck is completely different to that covered by the present invention. For example, in Buck, only certain amino acid residues can be accessed by the photoexcited dye to enhance the signal (page 5145, 2nd column, 2nd paragraph). The DNP of the present invention can enhance the polarization of all NMR active nuclei in a sample, and therefore has broader application. Moreover, a degree of hyperpolarisation of the accessible NMR active nuclei is in excess of 0.1% is not possible with the method of Buck. Applicant respectfully submits therefore that going from the photochemically-induced DNP method of Buck to the DNP method of the present invention is not merely a matter of discovering the optimum or workable ranges, as suggested by the Examiner. The polarization method of revised claim 1 clearly does not encompass the photoexcitation method disclosed by Buck.

Applicant respectfully submits that neither Yu nor Buck disclose an assay method, as would have been understood by the skilled person at the time of the invention, wherein said assay method uses an NMR active nucleus as an indicator, as covered by claim 1 of the present invention.

In addition, if the method of polarization enhancement of Buck was applied to NMR spectroscopy method of Yu, an enhancement in polarization would be achieved, but not to the level covered by present claim 1.

Therefore, Applicant respectfully submits that the combined teachings of Yu and Buck do not lead to a method falling within the terms of present claim 1, which is inventive over Yu in view of Buck. Since claims 3-6, 8-9, 11-15, 20, 27 and 30 all depend either directly or indirectly on claim 1, Applicant respectfully submits that these claims are also inventive over Yu in view of Buck. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 10 is rejected under 35 USC 103(a) as being unpatentable over Yu in view of Buck, and in further view of Katahira *et al* ("NMR Studies of G:A mismatches in Oligodeoxyribonucleotide Duplexes Modeled after Ribosomes" Nucleic Acids Research 1993; 21(23): 5418-24). This rejection is respectfully traversed.

Applicant respectfully submits, as outlined above, that Yu in view of Buck does not teach the invention substantially as claimed.

Katahira teaches that photochemically induced DNP can be used in an NMR method to observe hybridization of nucleic acids. As submitted above in relation to Buck, DNP carried out by photochemical induction cannot be broadly applied, and cannot achieve the polarization levels encompassed by the present claims. Applicant therefore submits that combining the teachings of Katahira with those of Yu and Buck, does not lead to claim 10 of the present invention, which is therefore believed to be inventive. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 24 and 25 are rejected under 35 USC 103(a) as being unpatentable over Yu, in view of Buck, and in further view of Obremski (6110749). Reconsideration is respectfully requested.

Applicant respectfully submits, as outlined above, that Yu in view of Buck does not teach the invention substantially as claimed.

Obremski provides multiplexed and multispot techniques that are useful for efficiently observing many samples at the same time. There is nothing in Obremski that teaches how to achieve the polarization levels encompassed by present claim 1. Obremski therefore does not bring the combined teachings of Yu and Buck any closer to the method encompassed by the present claim 1. Applicant therefore submits that claims 24 and 25 are inventive over Yu, in view of Buck, and in further view of Obremski. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 26 is rejected under 35 USC 103(a) as being unpatentable over Yu in view of Buck, in further view of Pines *et al* (6426058). This rejection is respectfully traversed.

Applicant respectfully submits, as outlined above, that Yu in view of Buck does not teach the invention substantially as claimed.

Pines disclose enhancement of NMR spectroscopy and magnetic resonance imaging using hyperpolarized noble gases. The non-noble gas NMR active nuclei of the method of Pines are polarized by contact with a hyperpolarized noble gas. There is no teaching in Pines of polarizing the NMR active nuclei using dynamic nuclear polarization comprising mixing the assay reagent with a paramagnetic species (DNP agent) and/or a free radical generator or other particles having associated free electrons.

Therefore, Applicant submits that the teachings of Pines do not bring the teachings of Yu combined with Buck to something encompassed by claim 26 of the present invention (dependent on claim 1). Present claim 26 is therefore believed to be inventive over the combined teachings of Yu, Buck and Pines. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 31 is rejected under 35 USC 103(a) as being unpatentable over Yu in view of Buck, in further view of Neild *et al* ("Uroscopy in the 21st Century: High-field NMR Spectroscopy" Neprol. Dial. Transplant. 1997; 12: 404-17). This rejection is respectfully traversed.

Applicant respectfully submits, as outlined above, that Yu in view of Buck does not teach the invention substantially as claimed.

Neild teaches that spin coupling provides an advantage for structural identification, and as such is an enhanced NMR spectroscopy method rather than an assay as would have been understood by the skilled person at the time of the present invention. Furthermore, there is no teaching in Neild of a DNP method to obtain the polarization level encompassed by present claim 1. Applicant therefore submits that the teachings of Neild do nothing to bring the combined teachings of Yu and Buck any closer to the invention encompassed by present claim 31, which is dependent on present claim 1. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the amendments and remarks hereinabove, Applicant respectfully submits that the instant application, including claims 1, 3-6, 8-15, 20, 24-27, 30 and 31, is in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,

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